Accompanying Documents

1. Marked-up copies of the originally presented claims incorporating the amendments made herein (Appendix A).

2. Clean copies of the pending claims after incorporation of the amendments made herein (Appendix B).

AMENDMENT

In the Specification:

Please add the following at page 7, line 2.

The patent or application file contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

In the Claims:

Please amend claim 9 as follows:

9. (Amended) The conjugate of claim 1, said isolated peptide sequence having at least about 50% homology with at least one of said SEQ ID Nos. 1-8.

REMARKS

Introductory Comments:

Claims 1, 2, 6-9, 35, 37, 38 and 42 were examined in the Office Action dated March 11, 2003.

Claims 1, 2, 6-9, 35, 37, 38 and 42 were rejected under 35 U.S.C. §112, first paragraph, as containing new matter.

Claims 9 and 42 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled.

Claims 9 and 42 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not supported by written description.

Claims 1, 2, 6-9, 35, 37, 38 and 42 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Gursoy *et al.* in view of Nagy *et al.*

These rejections are believed to be overcome in part by the above amendments and are otherwise traversed for the reasons discussed below.

Applicants acknowledge with appreciation the withdrawal of U.S.C. §112, first and second paragraph rejections for claims 1-3, 6-8, and 35-38.

Overview of the Above Amendments:

The specification has been amended to recite that at least one drawing executed in color is included, as requested by the Examiner. The amendment finds support in the drawings as originally filed.

Claim 9 has been amended to correct for dependency.

Accordingly, no new matter has been added by way of this amendment and the entry thereof is respectfully requested. Claims 1-2, 6-9, 35, 37–38, and 42 are presently pending.

Addressing the Examiner's Rejections

Rejections Under 35 U.S.C. §112, First Paragraph

(a) The Examiner rejected claims 1, 2, 6-9, 35, 37-38, and 42 under 35 U.S.C. §112, first paragraph, for allegedly containing new matter. The Examiner states that the specification and the claims as originally filed do not support "Xaa is penicillamine" for SEQ ID Nos: 1 and 3-8.

Applicants traverse the rejection. Sequence listing for SEQ ID Nos.: 1 and 5 do not contain the recitation that Xaa is penicillamine. Figure 7 illustrates the two different forms of an MTX-cIBR conjugate, where position 1 is shown to be Pen. Therefore, these sequences were improperly rejected.

Applicants at page 4, lines 7-14 of the specification state the following:

> "SEQ ID NO. 2 was synthesized as a 12-residue peptide containing 10 amino acid residues (Ile^{237} – Gly^{246}) from the "insert" (I)-domain of LFA-1 which is known to contain residues for ICAM-1 binding (Benedict et al., 1994).

> Penicillamine (Pen) and cysteine (Cys) residues were then added to the N- and C-termini (Benedict et al., 1994) to form cyclic peptides via a disulfide bond between the Pen1 and Cys12 residues. The formation of this cyclic peptides restricts the peptide conformation to produce a conformational stability, thereby providing better selectivity for cell surface receptors than its linear counterpart (Siahaan et al., 1996)."

The applicants thus teach that cyclic peptides, cLAB.L, cLAB.C, cLAB.R, cIBL, cIBC. and cIBR, referred to as SEQ ID Nos: 2, 3, 4, 6, 7, and 8, are cyclized by adding a Pen to the N-terminus, as shown by SEQ ID Nos. 2 and 8. The specification as filed thus provides support for the N-terminus being penicillamine for the cyclic peptides. Further, U.S. Patent No. 5,843,855 and Siahaan et al., (1996) "Counter receptor binding domains that block or enhance binding to LFA-1 or ICAM-1," in *Peptides: Chemistry, Structure and Biology*, Kaumaya and Hodges (Eds.), Mayflower Scientific, Kingswinford, England, pp. 792-793, cited in the specification and incorporated by reference teaches cyclic ICAM and LFA peptides having an N-terminus penicillamine as does U.S. Patent No. 6,075,004. The recitation of "Xaa is penicillamine" is thus not new added matter since the specification and claims as originally filed support the recitation. The Examiner is therefore respectfully requested to withdraw the rejection.

(b) Claims 9 and 42 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled.

The test for enablement is "whether one skilled in the art could make or use the claimed invention from the disclosure in the patent coupled with information known in the art without undue experimentation." United States v Telectronics, Inc. 8 USPQ2d 1217 (Fed. Cir. 1988); In re Wands, 8 USPQ2d 1400 (Fed Cir. 1988). Thus, in order to satisfy Section 112 regarding enablement, the specification need only set forth such information as is sufficient to allow one of ordinary skill in the art to make and use the invention. How such a teaching is accomplished, either by the use of illustrative examples or by broad terminology, is of no importance since a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of §112 unless there is reason

to doubt the objective truth of the statements relied upon therein for enabling support (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971)). The burden is on the Office to explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the applicants' claim: the reasoning must be supported by current literature as a whole and the Office must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). The Office has failed to provide adequate evidence to support the present rejection. Without such evidence, a rejection under 35 U.S.C. §112, first paragraph for lack of enablement cannot be sustained.

Applicants traverse the rejection. Claim 9, as amended, depends from claim 1. Claim 1 recites that the isolated peptide is selected from the group consisting of SEQ ID Nos. 1-8. The specification, at page 8, line 10 to page 10, line 9 details how to get 50% sequence identity. Given the disclosure and the sequences of SEQ ID Nos.: 1-8, one of ordinary skill in the art would be able to obtain a sequence having 50% identity to SEQ ID Nos. 1-8. Further, the specification provides detailed instructions for obtaining a drug peptide conjugate in Example 2. Thus, following the instructions provided in the specification, one of skill in the art would be able to make a drug-ICAM-1 and LFA-1 conjugate without undue experimentation where the peptide has 50% sequence identity to SEQ ID Nos. 1-8.

Claim 42 recites a peptide-drug conjugate where the peptide portion is obtained from the ICAM-1 or the LFA-1 sequences. The claim further recites structural limitation that the peptide is characterized by binding to LFA-1 and ICAM-1 receptors on leukocytes and by being internalized by cells expressing at least one of said receptors. As discussed above, the specification provides detailed description for obtaining a peptide from the ICAM-1 and LFA-1 sequences and for conjugating the drug to the selected peptide. Further, the specification at page 11, line 30 to page 16, line 36, discloses methods of characterizing the binding of the selected peptide to the receptor. The methods include antibody binding experiments, fluorescence and confocal microscopy studies, inhibition of antibody binding to the receptors by the selected peptides, effects of activation time and activators on binding, and the effects of temperature and divalent

cations on binding. Thus, a skilled artisan in the art would be able to characterize the binding of the selected peptide to the LFA or ICAM receptors of leukocytes without undue experimentation. Further, the specification at page 17, lines 1-11 describes methods for determining if the bound peptide is internalized. In the Examples, the applicants have provided detailed steps for determining if the peptide is internalized, and Figure 6 illustrates the binding and internalization of the peptides into the cells, as well as the distribution of the peptide within the cytoplasm of the cell (Figure 6e) compared to the cell periphery (Figure 6f). Thus, one of skill in art could follow the applicants specification and examples to determine if the peptide was internalized and the invention of claims 9 and 42 are enabled. The Examiner has provided no reason to doublt that the invention is not enabled. Therefore, the Examiner is respectfully requested to withdraw the rejection.

(c) The Examiner has rejected claims 9 and 42 under 35 U.S.C. §112, first paragraph, as allegedly not supported by written description. Examiner states that the applicants have not addressed the 50% homology issue in claim 9 or the conjugate of claim 42 where any peptide derived from ICAM-1 or LFA-1 could be used.

Applicants traverse the rejection. It appears that the Examiner is rejecting the claims because every sequence encompassed by the claims has not been literally written in the specification. This is not the test the applicants need to meet in order to satisfy the requirements of 35 U.S.C. §112, first paragraph. The test is whether one of skill in the art would understand that the applicants had possession of the invention at the time of application. It is axiomatic that compliance with the written description requirement of 35 USC §112, first paragraph only requires that the application contain sufficient disclosure, either expressly or inherently, to make clear to persons skilled in the art that the applicants were in possession of the subject matter claimed. See, e.g., *In re Mott*, 190 USPQ 536, 541 (CCPA 1976); and *Ex parte Harvey*, 3 USPQ2d 1626, 1627 (BOPAI 1987). The specification also preferably excludes what is commonly known. The applicants disclose the specific sequences of SEQ ID Nos.: 1-8. Further, the applicants at page 8, line 10 to page 10, line 9 details how to get 50% sequence identity. Thus, one of

skill in the art would understand that the applicants possessed sequences having 50% identity to SEQ ID Nos. 1-8. Similarly for claim 42, the applicants disclose LFA and ICAM sequences, disclose the selection peptide having SEQ ID Nos. 1-8 from those sequences and that the selected peptides bind to the LFA or ICAM receptors and are internalized. By providing a representative sample of 8 sequences selected from the ICAM or LFA sequences that can bind to the receptors and that can be internalized, the applicants have shown that they had possession of the invention of claim 42. It is not necessary to recite every possible sequence that could have been selected. Therefore, the Examiner is respectfully requested to withdraw the rejection.

Rejections of the Claims Under 35 U.S.C. §103

The Examiner has rejected claims 1, 2, 6-9, 35, 37-38, and 42 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Gursoy *et al.* in view of Nagy *et al.*

Summary of the Invention

Applicants' invention provides compositions that bind to the receptors on the surface of leukocytes and are internalized by the leukocytes (p 4, line 34 to p 6, line 34; and p 22, line 15 to p. 23, line 8 of the specification). These compositions include peptide molecules that bind to the LFA-1 and ICAM-1 receptors on leukocytes, where the peptides are derived from the ICAM-1 and LFA-1 sequences, respectively (p 2, lines 32-36). The selected peptides can be linear or cyclic, where a Pen and a Cys residue are added to the N- and C-termini of the selected sequence to form the cyclic peptide via a disulfide bond (p. 4, lines 7-14). The peptides can also be conjugated to drugs, such as cytotoxic drugs. The drugs can then be delivered specifically to activated leukocytes. The peptide-drug conjugates are internalized by the activated leukocytes and the cytotoxic drugs exert its toxic affect in a cell-specific manner without significant toxicity to other cells (p. 5, lines 19-35). The inventive compositions thus find use for cell-specific delivery of drugs. Further, the increased potency and selectivity of the inventive peptide-drug conjugate permits administration of a lower dosage of drugs with fewer side effects.

Argument

1. The combination of Gursoy and Nagy is based on improper hindsight.

The applicants traverse the rejections and supporting remarks as the references cited by the Office do not teach or suggest the claimed invention. In order to render claims obvious, the burden is on the Office to establish a *prima facie* case of obviousness for which three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references. Second, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all the claim limitations. The teachings or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The examiner's rejection is improper because there is no motivation (outside applicants' own disclosure) to modify or combine the teachings of Gursoy and Nagy to obtain the specific peptide drug conjugates of claims 1, 2, 6-9, 35, 37-38, and 42.

Claim 1 recites compositions comprising a drug and an isolated peptide sequence derived from LFA-1 and ICAM-1 receptor sequences. Claims 6-8 recite the drug for conjugation, with methotrexate as the species. Thus, claims 1, 2, 6-9, 35, 37-38 and 42 are limited to species of peptides and drugs, i.e., those peptides that are specifically recited in claim 1.

The Examiner's §103(a) rejection relies on combining Gursoy's generic teaching of targeted drug delivery to leukocytes with Nagy's teachings of conjugating peptide hormones with methotrexate to target prostate, breast, and pancreatic tumors.

The combination is impermissible hindsight based on applicants' own disclosure. As the Examiner acknowledges, Gursoy does not specifically teach the use of methotrexate as the drug. This fact, coupled with the silence of the secondary reference on the use of the particular sequences claims renders the rejection suspect. *See Ex parte Roth*, Appeal No. 1996-2756 at pp. 5-6.

There is nothing in the Nagy reference to suggest that an ordinary skilled artisan would read its disclosure as teaching peptides other than hormones, such as leutinizing

hormone releasing hormones (LH-RH) somatostatin and bombesin, for use in conjugation with methotrexate. Applicants submit that the teachings of Nagy identified in support of the Examiner's combination instead would be interpreted by one of ordinary skill in the art as pertaining specifically to LH-RH peptides, and more broadly to hormone peptides. The Nagy reference section on targeting supports this conclusion:

> "Various attempts have been made in our laboratory to use peptide hormone "carriers" for targeting different types of cytotoxic molecules to prostate, breast, and pancreatic tumors (8-13)." (p. 6375, first paragraph under discussion).

All the conjugates in the authors' papers, referenced as 8-11, pertain to hormone peptides. Thus, the references in Nagy to peptides are all tied to hormones, specifically LH-RH. There is nothing to suggest that one of ordinary skill reading Nagy would interpret its teaching in the expansive manner suggest by the Examiner to include all peptides, and so combine them with those of Gursoy. Instead, the combination is motivated by applicants' own disclosure and so cannot be relied upon to make out a *prima facie* case of obviousness. Accordingly, claims 1, 2, 6-8, 35, and 37-39 are patentable over the cited art.

The Examiner states that conclusion of obviousness is necessarily a reconstruction based upon hindsight reasoning and permissible as long as the knowledge gleaned from the applicants' disclosure is not used. With all due respect, the applicants disagree. If, as the Examiner has done, the term "peptide" in Nagy is read to mean all known or knowable peptides and the term "drug" in Gursoy is read to mean all drugs, the possible combinations of the peptide and the drug provides a large number of conjugates from which a choice could be made. Therefore, the choice of eight sequences of claim 1 that are used to make the conjugate from the large number of possible conjugates is unobvious. As stated by the Court of Appeals for the Federal Circuit *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." The only way to reach the conclusion of obviousness, given the large number of possibilities, is by using the applicants' disclosure as a blue print. Because the

combination of Gursoy and Nagy results in a very large number of possible conjugates, they fail to render obvious claims to the specific SEQ ID Nos. 1-8 conjugated to a drug.

The Examiner further states that the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results. The applicants disagree that the cited references, when combined, provide an expectation of success. Conjugation of methotrexate to N-terminus of ICAM-1 peptides may change the conformation of the cIBR peptide; Gursoy does not consider the conformational issue. This change of conformation may eliminate the recognition of the cIBR peptide by LFA-1 receptor on activated T-cells. Thus, prior to the applicants' invention, there was a possibility that the ICAM-drug conjugates would not recognize the target LFA-1 receptors, would not bind to the cells , and would not be internalized. However, the applicants results provide evidence that conjugation does not affect binding of the methotrexate -cIBR conjugate to LFA-1. The applicants showed that the structure of the active portion of the cIBR did not change when it was conjugated to methotrexate. Conjugation can also eliminate the activity of the drug. The applicants provided experimental evidence that showed conjugate did not eliminate the activity of methotrexate (drug). This can not be predicted by Gursoy or Nagy when taken separately or when combined. Nagy cyclized the LH-RH peptides using two terminal Cys residues – they did not use penicillamine (Pen) at the N-terminus (residue 1). Pen residue restricts the rotation of the disulfide bond in the cyclic peptide, which Cys residue cannot. The use of Pen at residue 1 restricts the conformation of the peptide and increases the conformational stability of the cyclic peptide. Nagy *et al.* use Cys at residue 1 and thus their peptides are conformationally more flexible then all the cyclic peptides that use Pen at residue 1, as disclosed by the applicants. Thus, the combination of the references does not provide an expectation of success that the conjugates would function as expected.

II. The combination of Gursoy and Nagy at best provides a generalized incentive insufficient to render obvious the claimed drug-peptide conjugates.

The combination of Gursoy with Nagy also fails to render obvious claims 1, 2, 6-9, 35, 37-38 and 42 because the references at best contain a generalized incentive to make

peptide-drug conjugate directed towards the ICAM-1 or the LFA-1 receptors. Nagy fails to provide any sequence information whatsoever regarding peptides selected from the ICAM-1 or LFA-1 sequences. The Nagy reference reports the sequence of somatostatin and two LH-RH peptides, and their selective coupling to either the α- or the γ-carboxyl group of the glutamic acid moiety in methotrexate (see Materials and Methods section). Nagy fails to teach or suggest the sequence of SEQ ID Nos. 1-8, or any peptide other than hormone peptides. Accordingly, because the disclosure of Nagy would fail to render obvious claims to specific sequences (SEQ ID Nos 1-8), it should not render obvious claims to conjugates of the specific sequences to methotrexate.

Gursoy similarly provides merely a generalized incentive to make the claimed peptide-drug conjugate. The last line of the Abstract states: "**In the future**, the binding and internalization of the cIBR peptide can be utilized as a method of targeted drug delivery to leukocytes for the treatment of leukocyte-related diseases." Applicants have added the emphasis to show that the Gursoy reference wished to convey that targeted drug delivery was a goal that required further experimentation. The conclusion denotes uncertainty as to the outcome rather than an expectation of success. Further, Gursoy never mentions that the drug could be methotrexate.

Given the absence of an ICAM-1 or LFA-1 peptide sequence in Nagy's disclosure, and the absence of any mention of methotrexate or any drug other than daunomycin, the combination fails to provide more than the most generalized type of incentive to make the drug-peptide conjugates of claim 1. The combination of Gursoy with Nagy therefore fails to make out a *prima facie* case of obviousness because "a general incentive does not make obvious a particular result, nor does the existence of techniques by which these efforts could be carried out." In re Deuel 35 USPQ2d 1210.

Further, the need to specifically target a receptor or a particular cell type are generalized scientific goals that cannot substitute for the particularity needed to establish a *prima facie* case of obviousness. The Examiner must show "reasons that the skilled artisan, confronted with the same problem as the inventor, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed." *In re Rouffet,* 47 USPQ2d at 1458, 1453 (Fed. Cir.

1998). Thus, the motivation to combine must be found within the references cited, and the required evidence cannot be substituted with a generalized scientific goal, as the Examiner has done in the present case. Thus, in the present case, the Examiner has not met the required specificity to establish a motivation to combine the references.

III. Objective Evidence

The Court of Appeals for the Federal Circuit, in Stratoflex, Inc. v. Aeroquip Corp., 218 USPQ 871, 879 (Fed. Cir. 1983), stated that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." Section 716.01(a) of the MPEP, citing In re Margolis, USPQ 940 (Fed. Cir. 1986), instructs the Examiners to always consider comparative data in the specification which is intended to illustrate the claimed invention in reaching a conclusion with regard to the obviousness of the claims.

In the present case, the comparative data shows that the conjugates have the advantage of being more toxic and have high potency thereby permitting lower dosage levels to be administered to patients. For example, the specification at page 2, lines 23-24, states that the applicants provide "an effect means of drug delivery to the cytoplasmic domain of leukocytes with improved efficacy and reduced toxicity in comparison to conventional methods of treatment." The specification, thus teaches that the selective targeting of cytotoxic drugs to leukocytes will reduce drug toxicity and increase drug efficacy. The specification, at page 5, lines 21-33, and page 6, lines 21-34, discloses that the conjugates of the cytotoxic drugs, such as methotrexate, to the peptides increases the potency and selectivity, thereby allowing lower dosage levels of the drugs to be administered to the patients resulting in fewer adverse effects. Figure 9 illustrates the comparative toxicities of different concentrations of methotrexate-cIBR conjugates and methotrexate alone, while Figure 10 compares the metabolic activity after treatment with methotrexate, the peptide cIBR, and methotrexate-cIBR conjugates. The toxicity experiments are discussed in detail at page 21, line 20, to page 23, line 8 of the specification. The drug-cIBR conjugate was shown to be selective for T-cells expressing LFA-1 only, and the toxicity was shown to be concentration dependent. Further, one

conclusion of the study was that the binding specificity provided selectivity for T-cells only, and the conjugate was 19 fold more toxic than methotrexate alone. Thus, the comparative data presented in the specification is consistent with the invention being nonobvious. The Examiner is therefore respectfully requested to withdraw the rejection.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Respectfully submitted,
Siahaan *et al.*

Date: May 12/2003

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Appendix A

Marked-up version showing amendments made.

In the Specification:

The specification was amended at page 7, line 2 to add the following:

--The patent or application file contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.--

In the Claims:

Claim 9 was amended as follows:

9. (Amended) The conjugate of claim [3] 1, said isolated peptide sequence having at least about 50% homology with at least one of said SEQ ID Nos. 1-8.